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The beneficial effects of Zn on Akt-mediated insulin and cell survival signaling pathways in diabetes

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ABSTRACT

Zinc is one of the essential trace elements and participates in numerous physiological processes. Abnormalities in zinc homeostasis often result in the pathogenesis of various chronic metabolic disorders, such as diabetes and its complications. Zinc has insulin-mimetic and anti-diabetic effects and deficiency has been shown to aggravate diabetes-induced oxidative stress and tissue injury in diabetic rodent models and human subjects with diabetes. Akt signaling pathway plays a central role in insulin-stimulated glucose metabolism and cell survival. Anti-diabetic effects of zinc are largely dependent on the activation of Akt signaling. Zn is also an inducer of metallothionein that plays important role in anti-oxidative stress and damage. However, the exact molecular mechanisms underlying zinc-induced activation of Akt signaling pathway remains to be elucidated. This review summarizes the recent advances in deciphering the possible mechanisms of zinc on Akt-mediated insulin and cell survival signaling pathways in diabetes conditions. Insights into the effects of zinc on epigenetic regulation and autophagy in diabetic nephropathy are also discussed in the latter part of this review.

1. Introduction

Zinc (Zn) is a mineral that is vital for various physiological processes, including enzyme action, stabilization of cell membrane, regulation of gene expression and cell signaling [1]. So far, more than 300 kinds of catalytically active Zn metalloproteins and more than 2000 Zn-dependent transcription factors have been discovered. The physiological and cellular Zn concentrations are largely regulated by metallothioneins (MTs), Zn importers (ZIPs, Zrt- and Irt-like proteins) and Zn transporters (ZnTs) [2,3], which participate in the absorption, excretion, transportation and intracellular storage of Zn. Abnormalities in Zn homeostasis, such as insufficient or deficiency of Zn, may be involved in the pathogenesis of numerous chronic diseases [4–6].

Diabetes mellitus (DM) is a disorder characterized by hyperglycemia as a consequence of decreased secretion or impaired action of insulin. Diabetes is reported to be frequently associated with various degrees of hypozincemia and/or hyperzincuria [7,8]. Zn have been demonstrated to exert insulin-like effects by facilitating signal transduction of insulin [9]. In addition, Zn also functions as a cofactor for a variety of enzymes and proteins that have anti-oxidative, anti-inflammatory and anti-apoptotic properties [10]. Supplementation with Zn has been proven to improve glycemic control as well as ameliorate chronic complications in both type 1 [11] (T1D) and 2 (T2D) diabetes [12,13], however, the exact molecular mechanisms has yet to be elucidated.

Akt signaling plays a central role in insulin-stimulated glucose metabolisms [14] and cell survival [15,16]. Zn has been demonstrated to activate Akt in a variety of cell lines *in vitro*, for instance, in human bronchial epithelial cells BEAS–2B [17], liver hepatocellular cells HepG2 [18], as well as in mouse embryonic fibroblast cells 3T3-L1 and rat adipocytes [19]. Additionally, Zn is able to induce Akt

Abbreviations: Akt2-KO, Akt2 gene deletion; CHO, Chinese hamster ovary; DM, diabetes mellitus; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; GLUT4, glucose transporter type-4; GS, glycogen synthase; GSK-3, glycogen synthase kinase 3; HbA1c, glycated hemoglobin; HDAC, histone deacetylase; IDDM, insulin-dependent diabetes mellitus; IGF-1R, insulin-like growth factor-1 receptor; IR, insulin receptor; IRSs, insulin receptor substrates; Mdm2, mouse double minute 2; MT, metallothionein; MTs, metallothioneins; Nrf2, nuclear factor-erythroid 2-related factor 2; PDK1, protein kinase 1; PGC-1α, PPAR-γ coactivator 1α; pH, pleckstrin homology; PI3 K, phosphoinositide-3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; PKB, protein kinase B; PPAR, peroxisome proliferator-activated receptor; PTEN, phosphatase and tensin homology deleted on chromosome 10; PTK, protein tyrosine kinase; PTP-1B, protein tyrosine phosphatase 1B; PTPases, protein tyrosine phosphatases; ROS, reactive oxygen species; RTKs, receptor tyrosine kinases; SH2, Src homology 2; Shc, Src homology collagen; SQSTM1, sequestosome 1; STZ, streptozotocin; TRB3, tribbles homolog 3; ZIPs, Zrt- and Irt-like proteins; Zn, zinc; ZnTs, Zn transporters

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phosphorylation in Chinese hamster ovary (CHO) cells, A10 vascular smooth muscle cells (A10VSMCs), and breast adenocarcinoma cells MCF-7 [20]. The activation of Akt signaling contributes to almost all aspects of glucose metabolisms, indicating the importance of Akt signaling pathway in the anti-diabetic effects of Zn.

Increasing evidence [21–23] have demonstrated that epigenetic mechanisms, i.e., DNA methylation, chromatin histone modification, and non-coding RNAs, may be involved in the pathophysiology of diabetic complications. Zn deprivation was found to induce histone 3 hyperacetylation at lysine 9 through the suppression of histone deacetylase (HDAC) activity, resulting in the nuclear translocation of NF-κB and reduced HDAC binding to NF-κB [24]. In addition, autophagy has been demonstrated to play an important role in the pathophysiology of diabetes and is essential for the maintenance of cellular homeostasis under stress conditions. A study using human hepatoma cells showed that Zn depletion caused a significant suppression of autophagy while Zn addition to medium stimulated autophagy in cells [25]. All of these findings implicate Zn insufficiency in the manifestation of diabetic complications.

In the present review, we summarize the recent advances based on the data from our own studies and others, with the focus on the following aspects: (1) the role of Zn in diabetes, (2) the effects of Zn on Akt-mediated insulin and cell survival signaling pathways in diabetic conditions, (3) the possible mechanisms by which Zn activates Akt signaling, and (4) the effects of Zn on epigenetic regulation and autophagy in diabetes and complications.

2. Zn homeostasis and diabetes

2.1. Zn deficiency in the pathology of both type 1 and type 2 diabetes

In T1D, there is a lack of insulin production. Zn deficiency is considered a critical element in the pathogenesis of diabetes, since it not only participates in the synthesis, storage and secretion of insulin, but also maintains the structural integrity of insulin [26]. Long-term exposure to low concentrations of Zn in drinking groundwater was reported to be associated with an increased risk of developing insulin-dependent diabetes or T1D [27]. A number of subsequent studies were consistent with these initial observations [28,29], which demonstrated an association between drinking water with low concentration of Zn and the incidence of childhood diabetes [29].

T2D is characterized by insulin resistance. Zn has insulin mimetic activity as well as antioxidant properties and Zn deficiency has been reported to be associated with insulin resistance [30,31]. Jou et al. confirmed that maternal Zn deficiency from 3-week preconception to 21-day postparturition resulted in decreased sensitivity to insulin in both female and male offspring even when they were fed a normal diet after weaning [32]. Another study observed that Zn deficiency increased leptin production in obese mice, indicating the importance of Zn dyshomeostasis in metabolic dysregulation in obesity [33]. The above evidence from animal models supports the notion that Zn deficiency may be associated with the development of T2D.

Recent studies have demonstrated that ZnT8 plays an important role in Zn homeostasis, and has been considered a new T1D autoantigen. ZnT8 transports Zn^{2+} from the β cell cytoplasm into insulin-secretory vesicles and plays an essential role in insulin storage and secretion. The incidence of ZnT8 antibody positivity was 65% in Argentinian population with T1D [34] and 50–60% in the Japanese population with acute onset of T1D [35]. Measuring ZnT8 antibody levels with the current panel of serologic markers for diabetes increased the detection of autoimmunity from 84.0 to 93.0% for new onset cases of T1D in Argentinians [34]. ZnT8 is encoded by the SLC30A8 gene. SLC30A8 polymorphic variant, rs13266634C/T, results in a missense R325W substitution, and was identified as susceptibility risk factor for T2D [36]. Mitchel et al. demonstrated that ZnT8 knockout mice had a marked reduction in β cell free Zn concentration, along with impaired glucose tolerance and abnormal granule morphology [37]. Furthermore, overexpressing the human W325 variant of ZnT8 in β cells resulted in improved glucose tolerance, which could be attributed to enhanced Zn secretion [38].

2.2. Anti-diabetic activity of Zn in animal models and diabetic patients

Supplementation of Zn in diets ameliorates glycemic control in various animal models [11,39,40]. In streptozotocin (STZ)-induced diabetic mice and OVE diabetic mice, we observed that Zn enhanced glucose utilization and improved hyperglycemic conditions [41,42]. Previous studies have also demonstrated enhanced insulin secretion and improved glucose tolerance in diabetic rats fed a dietary Zn supplement [43]. With regards to T2D, the relevant animal studies demonstrating the beneficial properties of Zn are sparse. Zn supplementation also facilitates the improvement of hyperglycemia as well as the reduction in fasting serum insulin in db/db obese mice [44]. These observations support the hypothesis that Zn may be helpful for glycemic control in both T1D and T2D.

The beneficial effects of Zn supplementation on diabetes are similarly observed in clinical studies, especially in T2D patients. Zn supplementation decreased glycated hemoglobin (HbA1c) and/or lipid levels and reduced urinal albumin excretion in T2D patients [45–47]. Supplementation of Zn also decreases serum homocysteine concentrations while promoting the intake of folic acid and vitamin B12 in patients with T2D and microalbuminuria [48]. Another study demonstrated the beneficial effects of Zn on improving insulin sensitivity without any obvious changes to serum leptin levels in normal glucose-tolerant obese women [49]. However, a recent study demonstrated that Zn treatment did not bring about any changes in insulin, HbA1c levels or glycemic control in T2D patients as compared with placebo group [50]. Substantiating these contrasting results will require further detailed work in both animal experimental models as well as human subjects.

2.3. The effect of Zn supplementation on diabetic complications

Diabetic complications result from long-term organ impairment caused by a variety of pathogenic factors. As we mentioned earlier, Zn serves as an essential cofactor for many important enzymes, transcriptional factors and metalloproteins. Zn deficiency may thus lead to the dysfunction of these enzymes or proteins under hyperglycemic conditions, eventually resulting in cell and organ impairment, which manifests as chronic diabetic complications. Zn acts as a cofactor for many antioxidant enzymes and can restore the altered glycoprotein components in the lung of T1D rats [51]. Zn supplementation has a beneficial effect on protecting against diabetic cardiomyopathy through the induction of MT, which has been proven in both animal models and human subjects [52–54]. Furthermore, Zn deficiency exacerbates diabetes-induced testicular apoptosis through the down-regulation of Akt expression in the testis [55,56]. Regarding diabetic neuropathy, Zn supplementation ameliorates the severity of neuropathy and improves nerve conduction velocity[57].

3. Zn and Akt-mediated insulin signaling pathways

3.1. Effects of Zn on Akt-mediated insulin signaling pathways

Insulin binding to its membrane insulin receptor (IR) is the initial step in the activation of the insulin signaling pathway. IR consists of two subunits: α-subunit and β-subunit, which are the- transmembrane and intracellular domains, respectively. By binding of insulin to its receptor, the α subunit induces a rapid conformational change to the receptor, which consequently results in trans-autophosphorylation of the tyrosine residues in the intracellular domain of the β subunit [58], followed by the catalytical activation of IR. The active IR promotes the

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